

REMARKS

Claim 34 has been amended to clarify that each of the at least two oncolytic viruses used in the claimed method selectively replicates in neoplastic cells having a different phenotype. Thus, for example, one oncolytic virus replicates in neoplastic cells with an interferon-resistance phenotype, wherein the other oncolytic virus replicates in neoplastic cells with an Rb-deficiency phenotype. Support may be found, for example, in the specification, for example, at paragraph [0038], page 8, which states in part "at least two viruses which can be used to phenotype tumors according to the present invention. The viruses are preferably selective for neoplasms with different phenotypes."

The Examiner is respectfully requested to enter the preceding amendment. No new matter is added by way of entry of these amendments.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 34-43 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement for use of mixtures of oncolytic viruses.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. MPEP §2164.01; *United States v. Teletronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Factors to be considered (MPEP 2164.01(a)) to support a determination that a disclosure is enabling and that undue experimentation is not required include, for example:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Evaluation of "undue experimentation" is not a single, simple factual determination, but is reached by weighing the above factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. MPEP 2164.01(a).

Breadth or scope of the claims; nature of the invention

The claimed invention is a method of diagnosing a neoplasm in an animal by phenotype, comprising (claim 34):

- (a) providing a biological sample from the animal, wherein the sample comprises neoplastic cells;
- (b) providing at least two oncolytic viruses, wherein each oncolytic virus selectively replicates in neoplastic cells having a phenotype selected from the group consisting of ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency; and wherein each of the at least two oncolytic viruses replicates in neoplastic cells having a different phenotype;
- (c) contacting the neoplastic cells in the sample with each of the at least two oncolytic viruses under conditions which allow each oncolytic virus to selectively replicate in the neoplastic cells having the phenotype for which each oncolytic virus is specific;
- (d) determining if each of the oncolytic viruses can selectively replicate in the neoplastic cells; and
- (e) diagnosing a neoplasm in the animal of a specific phenotype according to the ability of each of the oncolytic viruses to selectively replicate in the neoplastic cells.

The claimed method provides at least two oncolytic viruses, wherein each oncolytic virus **selectively replicates** in neoplastic cells having a phenotype selected from the group consisting of ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency. Further, each of the at least two oncolytic viruses replicates in neoplastic cells having a **different** phenotype. Thus, for example, one oncolytic virus replicates in neoplastic cells with an interferon-resistance phenotype, wherein the other oncolytic virus replicates in neoplastic cells with an Rb-deficiency phenotype. The claimed method also includes the use of conditions which allow each oncolytic virus to selectively replicate in the neoplastic cells having the phenotype for which each oncolytic virus is specific.

State of the prior art

The state of the prior art is that certain oncolytic viruses can selectively replicate in neoplastic cells having a particular phenotype.

Level of ordinary skill in the art

The level of ordinary skill in the art is high, and one of ordinary skill in the art routinely conducts a significant amount of experimentation.

Predictability, working examples and amount of guidance in the specification

The Examiner alleges that the specification does not describe how to use more than one oncolytic virus to differentiate the phenotype of a tumor. The Examiner alleges that, for example, oncolytic herpes virus G207 and adenovirus ONYX-015 can replicate in both ras and/or p53 mutated cells. The Examiner alleges that a person skilled in the art would consequently not be able to determine the phenotype of the cell just by observing the cell's death after one or more oncolytic viruses are administered according to the rejected claims.

Claim 34 has been amended to clarify that each of the at least two oncolytic viruses used in the claimed method selectively replicates in neoplastic cells having a different phenotype. As supported by the specification, for example, at least at paragraph [0038], page 8, “[t]he viruses are preferably selective for neoplasms with different phenotypes.” Using the guidance provided by the specification those of skill in the art can readily determine if the neoplastic cells have one or more of the phenotypes selected from the group consisting of ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency by using oncolytic viruses that selectively replicate in neoplastic cells with one of these phenotypes. Thus, each virus selectively replicates in neoplastic cells with one phenotype.

The claimed method can be performed, for example, in separate experiments for each oncolytic virus, where each experiment follows the guidance of Example 1 of the present specification. The claimed method can also be performed, for example, by using a mixture of the oncolytic viruses, because replication of the viruses can be detected using detection means specific for particular viruses:

The detection means can be a pair of primers specific for the nucleic acid of the reovirus, and may optionally include reagents for PCR. The detection means can also be an antibody specific for a reovirus protein, as well as accompanying reagents such as secondary antibodies. The detection means can further be slides and dyes suitable for observing the morphology of infected cells under the microscope, or virus culture media and cells that can be used to determine the titer of the reovirus. (page 7, paragraph [0037])

An "oncolytic virus" is a virus that selectively kills neoplastic cells. Killing of the neoplastic cells can be detected by any method established in the art, such as determining viable cell count, cytopathic effect, apoptosis of the neoplastic cells, synthesis of viral proteins in the neoplastic cells (e.g., by metabolic labeling, Western analysis of viral proteins, or reverse transcription polymerase chain reaction of viral genes necessary for replication), or reduction in size of a tumor. (page 11, paragraph [0053])

Thus, one of ordinary skill in the art can conduct the claimed method in separate experiments for each oncolytic virus or in a single experiment using mixtures of the oncolytic viruses and the cells in combination with detection means specific for each oncolytic virus.

The viruses of the Examiner's argument are not selective and cannot replicate in neoplastic cells having different phenotypes. In contrast, the claimed method comprises using oncolytic viruses that selectively replicate in neoplastic cells to allow diagnosing a neoplasm in the animal of a specific phenotype according to the ability of each of the oncolytic viruses to replicate in the neoplastic cells. Thus, the Examiner's argument is founded on an incorrect assumption, i.e., that the claims permit the use of viruses that are not selective.

Further, the Examiner states that a person skilled in the art would not be able to determine the phenotype of a neoplasm when using mixtures of two oncolytic viruses to differentiate the phenotype of a tumor, because both viruses will replicate. This aspect of the Examiner's argument incorrectly assumes that viral replication is only detected via cell death. However, as noted above, the specification provides detection means that are specific to particular viruses and that can selectively detect the replication of each oncolytic virus if the method is conducted using a mixture of oncolytic viruses. Thus one of ordinary skill in the art can perform the claimed invention using mixtures of different oncolytic viruses.

In addition, the claimed method can be used to diagnose neoplastic cells having multiple phenotypes, such as cells with ras pathway activation and p53-deficiency phenotypes (ras/p53 cells). For example, the method can use an oncolytic virus that selectively replicates in

neoplastic cells having the ras-pathway activation phenotype and a different oncolytic virus that selectively replicates in neoplastic cells having the p53-deficiency phenotype, such viruses are readily apparent to one of ordinary skill in the art. According to the claimed method, the ras/p53 cells are contacted with each of the oncolytic viruses under conditions which allow each oncolytic virus to selectively replicate in the neoplastic cells. As discussed above, one of ordinary skill in the art can easily determine whether one or both of the oncolytic viruses replicate in the ras/p53 cells. Thus, the skilled artisan could diagnose a neoplasm having both the ras and p53 phenotypes, according to the ability of each of the oncolytic viruses to replicate in the exemplary ras/p53 cells.

Quantity of experimentation needed to make or use the invention based on the disclosure

As noted above, the level of skill in the art is high, and a person of ordinary skill in the art routinely conducts significant amounts of experimentation. As discussed above, the claimed method can be performed, for example, in separate experiments for each oncolytic virus, where each experiment follows the guidance of Example 1 of the present specification. Moreover, as noted above, multiple detection means for determining viral replication, including detection means specific to particular oncolytic viruses, permits the use of a mixture of least two oncolytic viruses. Consequently, the amount of experimentation needed to perform the claimed method is small and is not significantly greater than the amount of experimentation ordinarily performed in the art and described in the specification. Therefore, one of ordinary skill in the art can make or use the claimed method using the guidance provided in the application, coupled with information known in the art, without undue experimentation.

Accordingly, Applicants submit that the specification fully enables the presently claimed method. Applicants respectfully request that the rejection of claims 34-43 under 35 U.S.C. § 112, first paragraph be withdrawn.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are respectfully requested. Allowance of the claims of this application at an early date is earnestly solicited. Applicants also encourage the Examiner to call the undersigned at (404) 724-2760 in the event that this may facilitate prosecution of the present application.

The required fee for filing a request for continued examination is being paid concurrently on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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